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What the Cannabis Industry Should Know About Plastic

Article

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I recently published two opinion pieces on what the cannabis industry should know about the role of stainless-steel equipment and glass container systems in contributing to elemental contaminants in cannabis consumer products[1, 2]. The feedback I received from those articles was very complementary and one of the many suggestions was to take a look at how plastic containers, bottles, bags, and components might contribute to heavy metal contamination. So, with that as background information, let's first take a closer look at how the pharmaceutical industry approached the problem and what evidence is out there in the public domain that indicates it could be an issue for the cannabis industry.

Plastic components and systems used in pharmaceutical manufacturing

Drug products can chemically interact with their associated packaging systems and/or the system's plastic materials and components of construction while the product is being manufactured, stored, or administered. It is therefore logical to assume that the magnitude of these interactions must not adversely affect the suitability of the drug product or the packaging system. While suitability for use includes several quality attributes of the packaged drug product and its performance, the impact of the plastic material on patient and consumer safety is critically important to evaluate.

To address these issues, the United States Pharmacopeial Convention (USP) has written five general chapters about the quality of plastic materials. They all cover slightly different areas, but their overall objective is to ensure that plastic packaging materials, components, and containers used in pharmaceutical applications are safe to use. The chapters include:

- **Chapter 661**: Plastic Packaging Systems and Their **Materials of Construction.**[3]
- Chapter 661.1: Plastic Materials of Construction.
  (Note: this is an update to 661 and is currently going through the approval process, so will not be official until Dec. 1st, 2025)[4]
- Chapter 661.2: Plastic Packaging Systems for Pharmaceutical Use.[5]
- Chapter 661.3: Plastic Components and Systems Used in Pharmaceutical Manufacturing.[6]
- Chapter 1661: Evaluation of Plastic Packaging and Manufacturing Systems and Their Materials of Construction with Respect to Their User Safety Impact.[7]

Potential for contaminants

To put this into perspective, it's important to understand that the pharmaceutical manufacturing process is the sum of all the steps that are required to convert raw materials into an active pharmaceutical ingredient (API) and then into a drug product (DP). Many of these steps use components that are either fully or partly constructed from plastics and polymers that will contain additives such as antioxidants, stabilizers, lubricants, plasticizers, and colorants, which could all potentially contain elemental impurities.

It is therefore likely that raw materials, process streams, production intermediates, APIs, and DPs will come into contact with one or more plastic components during the manufacturing process, resulting in process-related impurities, which have the potential to alter the quality of the pharmaceutical product. These interactions must be such that neither the production process nor the suitability for use of the drug substance or product is adversely affected.

The effect of these interactions on the quality and safety of drug products and the testing of these materials is covered specifically in Chapters1661 and 661.3, which address the suitability of plastic components used in the manufacture of both pharmaceutical and biopharmaceutical APIs and DPs. Although the manufacturing process may involve circumstances where plastic components are in contact with a wide variety of materials, this chapter is applicable mainly to those that involve liquid storage, process streams, and intermediates due to the expected increased degree of interaction with those liquids.

Manufacturers' responsibility

Drug manufacturers are responsible for establishing that these plastic components and systems are suited for their intended use by implementing a comprehensive risk assessment approach to ensure that they have been appropriately tested and that the test results have been fully evaluated. As a result, they must ensure that components and systems are chemically suited for their intended use with respect to safety by meeting the following criteria:

- The components are constructed from well-characterized materials that have been intentionally chosen for use as established by the test methods included in Plastic Materials of Construction.
- The general physicochemical properties of the components have been established.
- The biological reactivity of the components has been appropriately established.
- The components have been established as safe by means of the appropriate chemical testing, such as extractables or leachables profiling and toxicological assessment of the test data.

Testing protocols

Given the diversity of materials and components used in the manufacturing process and the widely varying conditions of contact experienced in manufacturing operations, it is not possible to establish a single extraction procedure that is a perfect match for every manufacturing circumstance. On the other hand, it is impractical to impose a large set of extraction conditions on the entire industry because, in most circumstances, it will not yield meaningful test results. The compromise therefore is to establish a standard extraction protocol based on a minimum set of conditions to assess both organic and inorganic impurities. Table 1, taken from Chapter 661.3, indicates which extraction conditions are appropriate for specific contaminants.

Table 1: Chemical extraction conditions used to evaluate the suitability of plastic components for the manufacture of drug products or substances[6]**.**

Extraction Solution	Extraction Method Per USP Chapter 661.3	Test Performed on Plastic Component or System
Water	Method C1	Absorbance, Acidity/Alkalinity, Total Organic Carbon (TOC)
0,1 N Hydrochloric Acid	Method C2	Extractable Metals
Acid/salt buffer (pH 3)	Method C3	Organic Extractables
Phosphate Buffer (pH 10)	Method C4	Organic Extractables
Ethanol/Water (50:50)	Method C5	Organic Extractables

The five model extraction methods (C1-C5) shown in Table 1 are intended to approximate the broad range of aqueous and organic liquids that may be encountered in the production of both pharmaceutical and biopharmaceutical manufacturing. The solvents represent water, 0.1 N hydrochloric acid, both low and high pH salt concentrations, and an organic solvent. As can be seen, one of the most important tests is to assess the level of extractable metals. In this procedure, depending on

the plastic material being tested (bottle, bag, container, tubing, etc.), the component is either filled with the test solution or a fixed amount of the plastic material is weighed into high purity borosilicate flask containing the test solution. The item is placed in an oven and heated to 55 °C ± 2 °C for 96 ± 2 hours. It's then allowed to cool and analyzed for all relevant metals by ICP-OES or ICP-MS using the analytical procedure described in USP Chapter 233[8].

So what metals are important?

It's important to emphasize that a well-characterized plastic is tested for its extractable levels of all metals that are known components of the plastic material. These metals could originate from the starting materials used to manufacture the plastic, the reagents used in the manufacturing process (e.g., catalysts), or the additives present in the plastic; such metals are termed "relevant metals". Additionally, relevant metals could also include those that are specified in compendial and regulatory documents as being relevant for plastic materials as defined in USP Chapter 232[9] and ICH Q3D Guidelines for Elemental Impurities[10]. However, although there are 24 metals defined in both these reference documents, as shown in Table 2, it might not be necessary to test for all of them depending on the intended method of delivery (oral, parenteral, inhalation, transdermal), the metal's toxicity (classification 1, 2A, 2B or 3), and/or the likelihood of finding it in the drug product/substance manufacturing process.

Table 2: USP Chapter 232 and ICH Q3D guidelines permitted daily exposure (PDE) limits for elemental impurities in drug compounds per method of administration[9, 10]. (Note: These limits are defined in µg/day – to convert to **µg/g** in the product/substance divide by the recommended daily dosage)

Element	Class	Oral PDE (µg/day)	Parenteral PDE (µg/day)	Inhalational PDE (**µg/day**)	Proposed Transdermal PDE (µg/day)
Cd	1	5	2	3	20
Pb	1	5	5	5	50
As	1	15	15	2	30
Hg	1	30	3	1	30
Co	2A	50	5	3	50
V	2A	100	10	1	100
Ni	2A	200	20	6	200
Tl	2B	8	8	8	8
Au	2B	300	300	3	3000
Pd	2B	100	10	1	100

Ir	2B	100	10	1	100
Os	2B	100	10	1	100
Rh	2B	100	10	1	100
Ru	2B	100	10	1	100
Se	2B	150	80	130	800
Ag	2B	150	15	7	150
Pt	2B	100	10	1	100
Li	3	550	250	25	2500
Sb	3	1200	90	20	900
Ba	3	1400	700	300	7000
Mo	3	3000	1500	10	15000
Cu	3	3000	300	30	3000
Sn	3	6000	600	60	6000
Cr	3	11000	1100	3	11000

So what metals impurities are in plastic materials?

So what metals are commonly found in plastics and polymers? There have been a number of studies in the open literature that cover the measurement of toxic metals in plastic materials, but they tend to focus on plastic labware like flasks, beakers, and tubing to better understand contamination issues when carrying out trace element analysis. One of the most important studies on this topic was the 1977 landmark paper published in Analytical Chemistry by John R. Moody and Richard M. Lindstrom. These two researchers evaluated some common laboratory container materials and showed that many of them are unsuitable for trace metal quantitation[11].

As a practitioner in the field of ICP-MS for almost 40 years, I have become well-versed in working in the ultra-trace environment and, as a result, know low quality borosilicate glass and plastic labware must be avoided at all costs[12]. That's why, when carrying out ultra-trace element analysis, only the highest purity plastic materials should be used to ensure the lowest achievable limits of quantitation (LOQ). It's well-recognized that some polymers such as propylene and polyethylene are manufactured from low-quality raw materials that can contain high levels of alkali, alkali earths, as well as transition and heavy metals. In addition, additives, plasticizers, coloring agents or mold releasing agents often contain other metals, such as silicon and zinc. This can be seen in the data in Table 3, which is taken from a chapter in my recent book on heavy metals in cannabis and hemp and is based on the Moody and Lindstrom study[13].

Table 3: Potential elemental impurities in common plastic materials

Material	Number of Elements	Total parts per million (ppm)	Typical impurities
Polystyrene (PS)	8	4	Na, Ti, Al
Tetrafluoroethylene (TFE)	24	19	Ca, Pb, Fe, Cu
Low-density polyethylene (LDPE)	18	23	Ca, Cl, K, Ti, Zn
Polycarbonate (PC)	10	85	Cl, Br, Al
Polymethyl pentene (PMP)	14	178	Ca, Mg, Zn
Fluorinated ethylene propylene (FEP)	25	241	K, Ca, Mg
Polypropylene (PP)	21	519	Cl, Mg, Ca
High-density polyethylene (HDPE)	22	654	Ca, Zn, Si

Other studies in the public domain

There have been a number of studies over the past few years to characterize the toxic metal content of various plastic materials used for the packaging of food products, but the data have been inconclusive as to whether the metals are actually leaching from the plastic into the food. However, they all show compelling evidence that there is a broad range of metallic impurities in most plastics and polymer materials[14, 15, 16,17]. One in particular that is worthy of mention is an excellent investigation published in the Journal of Environmental Health Science and Engineering entitled, “Determination of the selected heavy metal and metalloid contents in various types of plastic bags”, which focused on the potential threat to public health from discharging millions of plastic bags into the environment and, in particular, the impact of toxic elemental pollutants contained in them[17]. The study looked at several clear and colored plastic bags made from polyethylene (PE), high density PE (HDPE), low-density PE (LDPE), and polyvinyl chloride (PVC) and carried out the analysis of a panel of toxic heavy metals using closed vessel microwave digestion and ICP-OES. Table 4 is one set of data taken from the investigation, which shows a panel of elemental impurities in mg/kg (ppm) in polythene bags. It can be seen that many of them are in the tens of ppm while some of the elements such as copper, zinc, and barium are in excess of 100 ppm. These data were not outliers because the other types of plastic bags gave similar results.

Table 4: A panel of elemental impurities found in polythene bags (results in mg/kg)[17]

Sample	Pb	Cr	Cd	As	Cu	Zn	Mn	Se	Ba
PE-1A	ND	ND	7.9	ND	10.4	8.0	20.1	1.9	0.1

PE-2A	0.3	67.3	ND	0.7	ND	16.5	0.9	ND	66.2
PE-3B	1.3	0.01	5.3	ND	28.5	ND	ND	7.2	0.01
PE-4B	11.7	5,1	ND	27.9	ND	38.2	9.4	ND	45.9
PE-5B	ND	10.2	ND	9.8	21.7	11.1	2.5	ND	318.4
PE-6B	24.8	ND	17.5	ND	95.6	106.8	14.6	14.3	33.6
PE-7B	1.2	ND	ND	1.6	5.5	19.2	4.9	ND	0.5
PE-8F	15.4	9.5	0.8	5.3	19.3	55.7	7.2	0.7	112.6
PE-9B	65.8	75.1	ND	ND	30.8	153.7	12.7	26.3	121.5

Implications for the cannabis and hemp industry

So, what does this tell us about the cannabis industry? Clearly the pharmaceutical industry is highly regulated, having gone through a 20-year approval process to finally end up with a list of 24 elemental impurities in drug products, based on the route of administration, the metal toxicity and likelihood of finding it somewhere in the manufacturing process. However, this was based on carrying out a comprehensive risk assessment study outlined in ICH Q3D (R2) guidelines, covering all aspects of the drug production process including manufacturing equipment, water purity, container closure systems, drug substances, and excipients, which the pharmaceutical industry has specifically addressed using the classic root cause fishbone diagram shown in Figure 1[10]. Evaluating the quality of plastic materials would be an integral part of the risk assessment process.

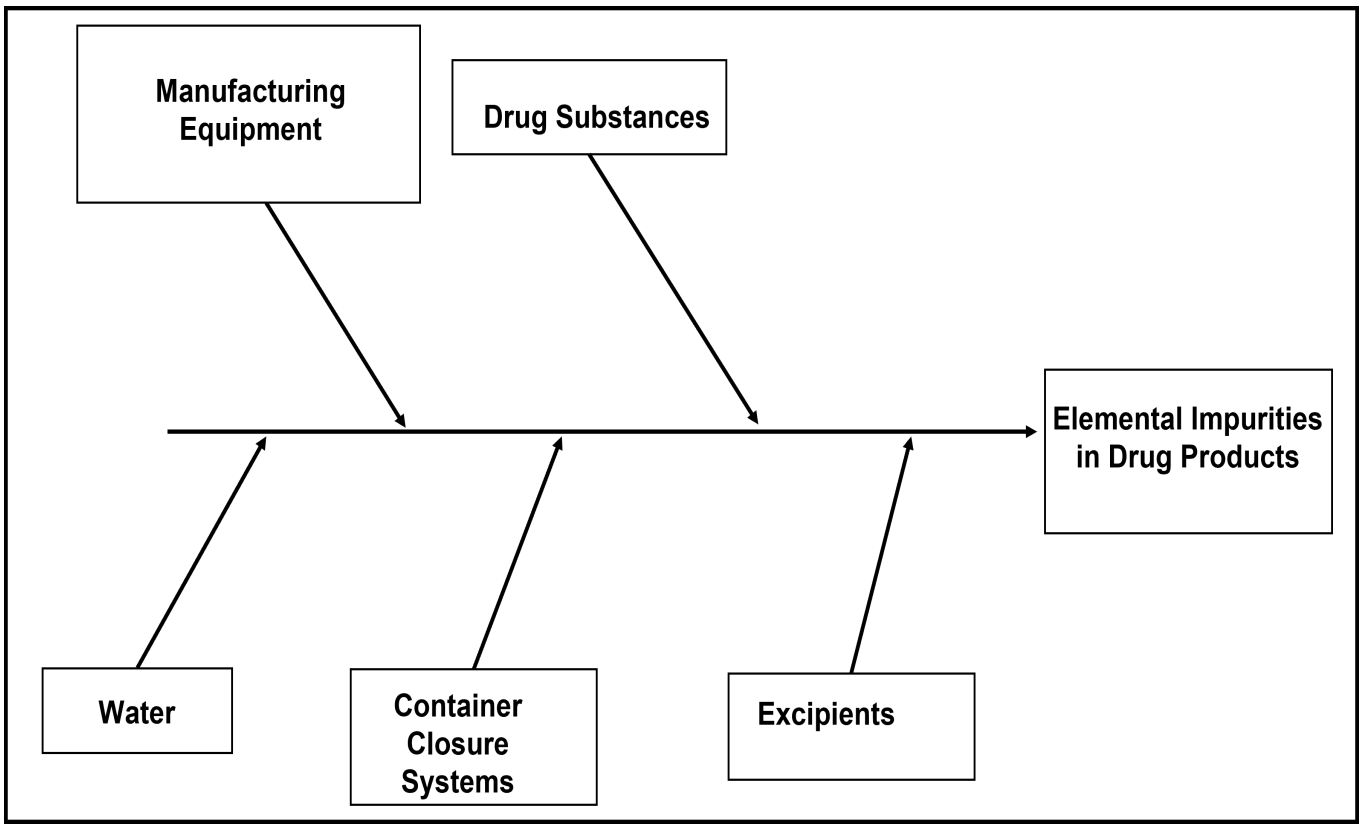

Figure 1: Classic fishbone diagram of the pharmaceutical manufacturing process to identify the root cause of a problem to better understand elemental impurities in drug products.[10]

So, could this approach be adopted by the cannabis industry? If each of the different areas of production including cultivation, extraction, manufacturing, packaging, and delivery processes would need to be characterized by a risk assessment study to identify all the potential heavy metals and elemental contaminants of concern in the final cannabis consumer products? Unfortunately, there has been no such risk assessment study carried out by the cannabis industry, so we don't know if it's feasible, although I propose a possible way of doing this in a recent publication[18]. It therefore begs the question, what if these plastic bags were taken through the extractable metals testing procedure described in USP Chapter 661.3 and filled with 0.1N HCl and heated to 55 °C ± 2 °C for 96 ± 2 hours? Would these metals be leached out? We have no way of knowing, but there's no question that if it happened in a pharmaceutical manufacturing plant, the company would be mandated to investigate because the FDA has oversight of the industry. However, if it occurred with a cannabis manufacturer, there is no requirement to carry out this testing procedure, so it would escape the scrutiny of the state regulators.

Final thoughts

It has been shown that both stainless steel and glass have the potential to contaminate cannabis and hemp consumer products, as demonstrated by my previous articles[1, 2]. In particular, the high levels of heavy metal particulates in unused THC vaping devices indicates that the metals are most probably derived from the corrosion of either the metal, glass, or plastic components, or perhaps a combination of all three[2]. However, with the current state-driven regulatory system, there is very little incentive to understand sources of heavy metals in the cannabis production process, or the end products including the role of plastic components, bottles, containers, and bags. There is a strong likelihood that some metals could be leaching out of them, especially if cannabinoid extracts and oils are stored in them for long periods, but there's not been enough testing to definitively make that conclusion. It would be relatively straight forward to come up with a suitable leaching procedure using common cannabinoid diluents/cutting agents, such as medium chain triglyceride (MCT) oil, glycerin, or propylene glycol, to study extractable metals in cannabis systems, but there are currently no regulations in place to address this problem. So, until the cannabis industry makes a decision to have a meaningful approach to risk assessment, we have no way of knowing if plastic materials are a potential source of elemental contamination. We can only assume that, when the industry eventually comes under the scrutiny of federal regulators, we might find out the answer. But, until then, we can only keep on asking the questions….and hope that someone is listening!

Further reading

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